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EXAMINER	
SASAN, ARADHANA	

ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
11/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/714,347	RICHARD ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15,17,18 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15,17,18 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 08/08/08 are acknowledged.

2. Claims 1-2, 4-15, 17-18 and 20 are included in the prosecution.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-2, 4, 7-13, 15, 17-18 and 20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yajima et al. JP 05-309261, in view of Gillberg-Laforce et al. (US 5,618,622) and Ezpeleta et al. (International Journal of Pharmaceutics, 131 (1996) 191-200).

The claimed invention is a method for producing microcapsules containing a material to be encapsulated, wherein the method comprises: (a) solubilizing at least one plant protein in an aqueous medium at a pH that is between 2 and 7 to obtain a solution comprising at least one solubilized plant protein; (b) centrifuging the solution of step (a) to obtain a supernatant and a pellet; (c) mixing the supernatant of step (b) with an aqueous solution comprising a polyelectrolyte having the opposite charge of that of the at least one plant protein to obtain a solution comprising at least one solubilized plant protein and a polyelectrolyte having the opposite charge of that of the at least one plant protein; and (d) coacervating the at least one solubilized plant protein and the

polyelectrolyte having an opposite charge to the at least one plant protein from the solution of step (c), in the presence of the material to be encapsulated, to form microcapsules comprising a complex coacervate of the plant protein and polyelectrolyte about the material to be encapsulated.

JP 05-309261 teaches the manufacture method of a microcapsule (Detailed Description, [0001]). A polycationic wall material and a polyanionic wall material are subjected to complex coacervation to produce microcapsules (Abstract). The complex coacervation method is disclosed (Detailed Description, [0002]). Wheat gluten extract is used as the poly cation wall membrane material in a microcapsule made by complex coacervation (Detailed Description, [0004]). Polyanion wall materials such as gum arabic, sodium alginate, and agar are disclosed (Detailed Description, [0008]).

JP 05-309261 does not expressly teach cationic polyelectrolytes or the use of glutaraldehyde as a crosslinking agent for hardening the microcapsules.

Gillberg-Laforce teaches polyelectrolytes that include chitosan and sodium carboxymethylcellulose (Col. 4, lines 38-41).

Ezpeleta teaches the formation of nanoparticles from gliadin (a vegetal protein fraction from wheat gluten) (Abstract). Chemical cross-linkage of nanoparticles with glutaraldehyde significantly increased the stability of the gliadin nanoparticles (Abstract). "Nanoparticulate carriers from vegetal macromolecules are a new approach which may present some advantages. Proteins are metabolizable and they can incorporate a wide variety of drugs in a relatively non-specific fashion" (Page 192, right hand column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a microcapsule with wheat protein extract by complex coacervation, as suggested by JP05309261A, combine it with the polyelectrolytes including chitosan and sodium carboxymethylcellulose, as taught by Gillberg-Laforce, and the use of glutaraldehyde as a crosslinking agent for gliadin nanoparticles, as taught by Ezpeleta, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Ezpeleta teaches that using plant proteins for producing nanoparticles has advantages of incorporating a wide variety of drugs (Page 192, right hand column). One with ordinary skill in the art would also be motivated to use plant proteins instead of the gelatin that is generally used in complex coacervation for producing microcapsules in order to have a non-animal origin protein source.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 1, the limitation of (step 1a) the method for producing microcapsules comprising solubilizing at least one plant protein would have been obvious over the complex coacervation used to produce gluten microcapsules as taught by JP 05-309261 (Abstract) and by the preparation of gliadin nanoparticles, as taught by Ezpeleta (Page 193, Section 2.2.2). The limitation of the pH of the aqueous medium in

which the plant protein is solubilized would have been obvious to one of ordinary skill in the art because during the process of routine experimentation, one would vary the pH of the medium in order to optimize the solubilization of the plant protein. The pH would be varied depending on the plant protein and the solvent chosen. The limitation of (step 1b) centrifuging the solution would have been obvious over the centrifugation taught by Ezpeleta (Page 193, right hand column). The limitation of (step 1c) mixing the supernatant with a polyelectrolyte having the opposite charge of that of the plant protein would have been obvious over the polyelectrolytes taught by Gillberg-Laforce (Col. 4, lines 38-41). The limitation of (step 1e) coacervating the solubilized plant protein and the polyelectrolyte in the presence of the material to be encapsulated would have been obvious over the complex coacervation used to produce gluten microcapsules as taught by JP 05-309261 (Abstract) and by the preparation of gliadin nanoparticles containing retinoic acid, as taught by Ezpeleta (Page 193, Section 2.2.2).

Regarding instant claim 2, the hardening of the microcapsules after coacervating would have been obvious over the crosslinking of nanoparticles with glutaraldehyde as taught Ezpeleta (Page 193, right hand column).

Regarding instant claim 4, the limitation of adding additional plant proteins to the supernatant would have been obvious over the complex coacervation used to produce gluten microcapsules as taught by JP 05-309261 (Abstract) and by the preparation of gliadin nanoparticles containing retinoic acid, as taught by Ezpeleta (Page 193, Section 2.2.2). During the process of routine optimization, one with ordinary skill in the art would modify the level of plant protein in the supernatant in order to optimize the desired size

or thickness of the microcapsules as well as to optimize the stability of the microcapsules with the desired material to be encapsulated.

Regarding instant claims 7-8, the plant protein would have been obvious over the wheat protein used in coacervated microcapsules as taught by JP05309261A (Abstract) and Ezpeleta (Abstract).

Regarding instant claims 9-10, the cationic polyelectrolyte and the anionic polyelectrolyte would have been obvious over the polyelectrolytes chitosan and sodium carboxymethylcellulose, as taught by Gillberg-Laforce (Col. 4, lines 38-41).

Regarding instant claims 11-13, the crosslinking agent would have been obvious over the glutaraldehyde taught by Ezpeleta (Abstract).

Regarding instant claims 15 and 17, the microcapsules would have been obvious over the microcapsules taught by JP05309261A (Abstract) and by Ezpeleta (Abstract).

Regarding instant claims 18 and 20, the limitation of a pharmaceutical composition comprising the microcapsules would have been obvious over the microcapsules comprising retinoic acid as taught by Ezpeleta (Abstract).

5. Claims 5-6 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yajima et al. JP 05-309261, in view of Gillberg-Laforce et al. (US 5,618,622), Ezpeleta et al. (International Journal of Pharmaceutics, 131 (1996) 191-200) and Kangas et al. (US 3,843,585).

The teachings of JP05309261A, Gillberg-Laforce and Ezpeleta are stated above.

JP05309261A, Gillberg-Laforce and Ezpeleta do not expressly teach the solubilizing step 1a that is carried out at a pH below the isoelectric pH of the at least one

plant protein, so that the at least one plant protein can be used as a cationic polyelectrolyte in the coacervating step.

Kangas teaches that "the amount of polyelectrolyte combined with the aqueous disperse system is an amount sufficient to coacervate the aqueous disperse system at pH which is below the isoelectric point of the polyelectrolyte and which is above the pH at which the anionizable groups of the disperse material begin to dissociate to form anions" (Col. 8, lines 20-26). "... The coacervated disperse material can be redispersed to a disperse system by adjusting pH of the coacervated system to value above the isoelectric point of the polyelectrolyte prior to curing or film formation of the coacervated disperse material" (Col. 8, line 65 to Col. 9, line 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a microcapsule with wheat protein extract by complex coacervation, as suggested by JP05309261A, combine it with the polyelectrolytes including chitosan and sodium carboxymethylcellulose, as taught by Gillberg-Laforce, and the use of glutaraldehyde as a crosslinking agent for gliadin nanoparticles, as taught by Ezpeleta, further combine it with the aqueous disperse system at a pH which is below the isoelectric point of the polyelectrolyte, as taught by Kangas, and produce the instant invention.

One of ordinary skill in the art would have done this because modifying the pH below the isoelectric pH of the wall material of a coacervated microcapsule is known in the art, as evidenced by the teaching of Kangas.

Regarding instant claim 5, the limitation of carrying out the solubilizing step at a pH below the isoelectric pH of the at least one plant protein would have been obvious over the aqueous disperse system at a pH which is below the isoelectric point of the polyelectrolyte, as taught by Kangas (Col. 8, lines 20-26).

Regarding instant claim 6, the limitation of carrying out the solubilizing step at a pH above the isoelectric pH of the at least one plant protein would have been obvious over the pH adjustment of the coacervated system to a value above the isoelectric point of the polyelectrolyte prior to curing or film formation of the coacervated disperse material" (Col. 8, line 65 to Col. 9, line 2).

6. Claim 14 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Yajima et al. JP 05-309261, in view of Gillberg-Laforce et al. (US 5,618,622), Ezpeleta et al. (International Journal of Pharmaceutics, 131 (1996) 191-200) and Lee et al. (Journal of Applied Polymer Science, Vol. 63, Issue 4, 425-432).

The teachings of JP05309261A, Gillberg-Laforce and Ezpeleta are stated above.

JP05309261A, Gillberg-Laforce and Ezpeleta do not expressly teach the use of acetic anhydride as the hardening agent.

Lee teaches hardening microcapsules containing the cationic polyelectrolyte chitosan by using acetic anhydride as the hardening agent (Journal of Applied Polymer Science 1997). Lee teaches that "chitosan, a cationic polysaccharide, was ... deacylated ... and followed by a homogenous reacylation with acetic anhydrides" (Abstract). It is further taught that polyelectrolyte complexes are formed when chitosan is complexed with an anionic polysaccharide (like sodium alginate) and drug

microencapsulation was the application of the polyelectrolyte complexes produced (Abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a microcapsule with wheat protein extract by complex coacervation, as suggested by JP05309261A, combine it with the polyelectrolytes including chitosan and sodium carboxymethylcellulose, as taught by Gillberg-Laforce, and the use of glutaraldehyde as a crosslinking agent for gliadin nanoparticles, as taught by Ezpeleta, further combine it with the use of acetic anhydride and chitosan, as taught by Lee, and produce the instant invention.

One of ordinary skill in the art would have done this because the addition of acetic anhydride allows the reacylation of chitosan (as taught by Lee), which further cross links or "hardens" the resultant microcapsule.

Regarding instant claim 14, the limitation of chitosan and acetic anhydride would have been obvious over the chitosan and acetic anhydride taught by Lee (Abstract).

Response to Arguments

Objection to claim 1

7. In light of Applicant's amendment of claim 1, the objection of 05/08/08 is withdrawn.

Rejection of claims under 35 USC § 103(a)

8. Applicant's arguments, see Page 6, filed 08/08/08, with respect to the rejection of claims 1-2, 4, 7-13, 15, 17-18 and 20 under 35 U.S.C. 103(a) as being unpatentable over Yajima et al. JP 05-309261, in view of Gillberg-Laforce et al. (US 5,618,622) and

Ezpeleta et al. (International Journal of Pharmaceutics, 131 (1996) 191-200) have been fully considered but are not persuasive.

Applicant argues that the term "polyelectrolyte" as defined by Gillberg-Laforce does not include proteins, and that the use of proteins may be undesirable in their invention.

This is not persuasive because the plant protein gluten is disclosed by Yajima and Gillberg-Laforce is used as a secondary reference that discloses polyelectrolytes. The secondary reference Gillberg-Laforce is used for the teaching that polyelectrolytes include chitosan and sodium carboxymethylcellulose and that polyelectrolytes produce large chain type ions in solutions (Col. 4, lines 31-33). One with ordinary skill in the art would use polyelectrolytes in the aqueous solution of Yajima in order to neutralize the charge of the plant protein.

Applicant argues that Ezpeleta does not disclose making nanoparticles without the presence of an organic solvent in the water and that Ezpeleta requires removal of the organic solvent from the solution in order to form the nanoparticles and uses desolvation to form the nanoparticles. Applicant argues that Ezpeleta does not use the process of coacervation, which is the process used in the Applicant's invention.

This is not persuasive because the primary reference, Yajima, teaches complex coacervation for producing gluten microcapsules. Ezpeleta is used as a secondary reference to cure the deficiency of glutaraldehyde as a crosslinking agent with the motivation of increasing the stability of the gliadin nanoparticles.

Applicant argues that there is no suggestion or motivation in Yajima, Gillberg-Laforce or Ezpeleta to modify or combine the reference teachings to obtain the method of the applicants' invention. Applicant argues that none of these references provide any suggestion or motivation to solubilize at least one plant protein in an aqueous medium at a pH that is between 2 and 7 to obtain a solution comprising at least one solubilized plant protein. Applicant argues that Yajima teaches away from using an aqueous solution.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine Yajima, Gillberg-Laforce and Ezpeleta is provided by Ezpeleta who teaches that using plant proteins for producing nanoparticles has advantages of incorporating a wide variety of drugs (Page 192, right hand column). Moreover, one with ordinary skill in the art would also be motivated to use plant proteins instead of the gelatin that is generally used in complex coacervation in order to have a non-animal origin protein source.

Applicant argues that one of ordinary skill in the art, upon reading Yajima would interpret that the preferable range of 5-10% ethanol indicates that 1-5% ethanol in water

is less effective than 5-10% ethanol in water and therefore some ethanol is needed for their process to be effective.

This is not persuasive because even if some ethanol is needed for the process of Yajima, one with ordinary skill in the art would consider the solution to be an aqueous solution. The term "comprises" in instant claim 1, is open language, and does not preclude an aqueous medium that has some ethanol in the process.

Applicant argues that Ezpeleta also teaches away from the use of an aqueous solution. Applicant also argues that neither Yajima, Gillberg-Laforce nor Ezpeleta teach or suggest solubilizing the plant protein in an aqueous medium.

This is not persuasive because Yajima, the primary reference, teaches complex coacervation with a gluten extract in a 1-20 volume % aqueous solution. Ezpeleta is used as a secondary reference to cure the deficiency of the use of glutaraldehyde as a crosslinking agent for hardening nanoparticles. The motivation to use Ezpeleta is the enhanced stability of the gliadin nanoparticles when glutaraldehyde is used.

Therefore, the rejection of 05/08/08 is maintained.

9. Applicant's arguments, see Page 11, filed 08/08/08, with respect to the rejection of claims 5-6 under 35 U.S.C. 103(a) as being unpatentable over Yajima et al. JP 05-309261, in view of Gillberg-Laforce et al. (US 5,618,622), Ezpeleta et al. (International Journal of Pharmaceutics, 131 (1996) 191-200) and Kangas et al. (US 3,843,585) have been fully considered but are not persuasive.

Applicant argues that Kangas does not overcome the deficiencies of Yajima, Gillberg-Laforce and Ezpeleta.

This is not persuasive because Kangas is used to cure the deficiency of the solubilizing step that is carried out at a pH below the isoelectric pH of the plant protein.

Applicant argues that the combination of references as cited in the Office Action uses various selected features from different references without considering the teachings of each reference to determine the relevance and motivation to use the reference. Applicant argues that while Ezpeleta teaches forming microparticles by the process of desolvation, there is nothing in the Office Action that explains why one of ordinary skill in the art would take the specific features recited in the Office Action that are used in desolvation and use them in a process that requires coacervation, where these two processes operate by totally different mechanisms. Applicant argues that Gillberg-Laforce is related to surface modified fibrous materials that are used as a filtration medium which is not in any way related to producing nanoparticles. Applicant argues that the Office Action provides no rationale for one of ordinary skill in the art to selectively choose using chitosan and sodium carboxymethylcellulose to produce nanoparticles from a reference on surface modified fibrous materials that are used as a filtration medium. Applicants believe this represents a classic case of "hindsight reconstruction."

It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the instant case, Yajima teaches a method of making a microcapsule with wheat protein extract by complex coacervation. Gillberg-Laforce teaches polyelectrolytes including chitosan and sodium carboxymethylcellulose. The use of glutaraldehyde as a crosslinking agent for gliadin nanoparticles is taught by Ezpeleta. An aqueous disperse system at a pH which is below the isoelectric point of the polyelectrolyte is taught by Kangas. All the claimed elements are found in Yajima, Gillberg-Laforce, Ezpeleta and Kangas, and one with ordinary skill in the art could have combined the elements and the combination would have yielded predictable results. See *KSR International Co. v. Teleflex Inc.*, 550 U.S. - , 82 USPQ2d 1385 (2007).

Therefore, the rejection of 05/08/08 is maintained.

Conclusion

10. No claims are allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615